Department of Chemistry, University of Pittsburgh

# The Synthesis of 9-Acridanylmethyl and 9-Acridinylmethyl Ketones

Chester S. Sheppard (1) and Robert Levine

A series of new 9-acridanylmethyl ketones has been prepared by the 9,10-addition of the sodium derivatives of a number of ketones to acridine. The 9-acridanylmethyl ketones were dehydrogenated to the corresponding 9-acridinylmethyl ketones by either acidic ferric chloride or lead tetraacetate. A route of more limited utility for the synthesis of 9-acridinylmethyl ketones involves the acylation of 9-acridinylmethyllithium with certain esters. The attempted ketonic cleavage of α-(9-acridinyl)-β-ketoesters such as ethyl α-(9-acridinyl)isonicotinoylacetate and ethyl α-(9-acridinyl)benzoylacetate is an unsatisfactory method for obtaining the corresponding 9-acridinylmethyl ketones since these ketones are cleaved to 9-methylacridine under mildly acidic or basic conditions.

For a number of years work has been in progress in this laboratory on the prototropic reactions of the isomeric picolines. Thus, it has been found that 4-picoline can be acylated (2,3) with a series of esters to give the corresponding 4-acylmethylpyridines in high yields.

The acylation of 4-picoline is of special interest in connection with the present study since it may be regarded as being structurally related to 9-methylacridine (I) and, under the appropriate basic conditions, it should be possible to acylate the 9-methyl group of I with esters to give a series of 9-acridinylmethyl ketones (III). Apparently such acylations are not described in the literature.

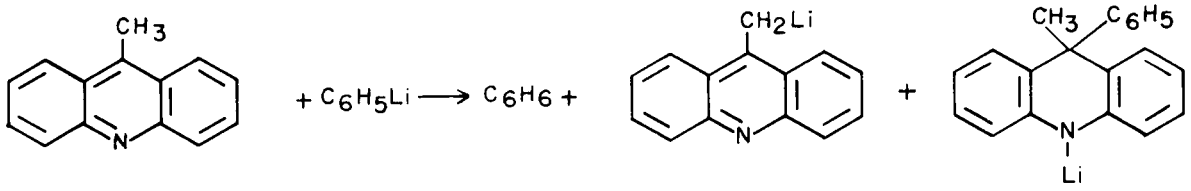
There are a number of reports which indicate that the hydrogen atoms of the methyl group of I are labile. For example, I undergoes a Mannich reaction (4), it condenses normally with aldehydes (5, 7) and it adds to ω-nitrostyrene (6). One very significant reaction involving the metalation of the methyl group of I was reported by Lettré *et al.* (8) who found that 9-cyanomethylacridine is obtained in 70% yield from the reaction of I, phenyllithium and phenylmethylcyanamide.

Although Ziegler and Zeiser (9) report that I is metalated exclusively on the methyl group by phenyllithium, we have found (eq. 1) that about 12% of the 9,10-addition product is also formed. Our present findings are not too surprising since it was observed earlier (2) that during the acylation of 4-picoline with methyl benzoate using phenyllithium as the condensing agent as much as 39% and 33% of the azomethine addition products 2-phenyl-4-methylpyridine and 2,6-diphenyl-4-methylpyridine, respectively, were isolated in addition to the desired 4-phenacylpyridine. In addition, it has been noted (10) that the reaction of 4-methylquinoline with phenyllithium gave the azomethine addition products 2-phenyl-4-methylquinoline (61-66%) and 2, 2-diphenyl-4-methyl-1, 2-dihydroquinoline (24-26%).

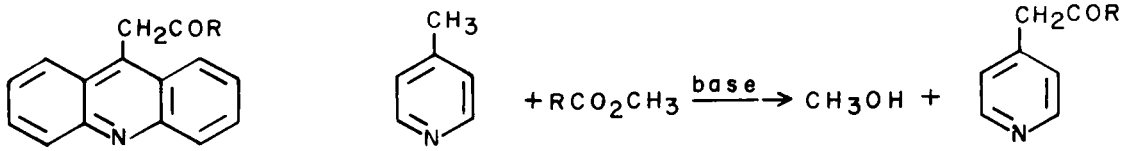
We now report that 9-methylacridine (I) has been acylated with four esters to give the corresponding 9-acridinylmethyl ketones in good to high yields (41-83%, Table I). Essentially the same yield, based on 9-methylacridine, of 9-phenacylacridine was obtained when a 1:1:1 or a 2:2:1 molar ratio of I to phenyllithium to methyl benzoate was employed. These results suggest that the mechanism of these acylations is similar to that described earlier for the base-induced acylations of 2-picoline (11) and 4-picoline (2). It can be summarized as follows. This scheme indicates that two moles of II are required to produce each mole of III since it is reasonable to assume that as rapidly as III is formed (equation 2) it should be converted to IV (equation 3) by an equivalent amount of II since the methylene hydrogen atoms of II would be expected to be very labile.

The reactions failed when the methyl or ethyl esters of acetic, pivalic and the three isomeric pyridine carboxylic acids were used as acylating agents. In all of these reactions, 9-17% yield of 9-methyl-9-phenylacridan was isolated and none of the esters were recovered. It is possible that when the isomeric methyl pyridinecarboxylates were the acylating esters, the ketonic products were actually formed and that they were cleaved in the strongly basic reaction medium. Thus, it was found that 9-picolinylmethylacridine (which was prepared by another method, *vide infra*) was decomposed by dilute sodium hydroxide to give I in 77.2% yield. It is probable that the acylation of II by ethyl pivalate failed for steric reasons and that the reaction between II and ethyl acetate was unsuccessful because of the possibility that II effected the self-condensation of the ester although no ethyl acetoacetate was actually isolated.

Since the direct synthesis of 9-acridinylmethyl ketones by the acylation of II with esters was successful in only four cases, another route to these ketones was sought. It has been shown (12) that certain compounds with very reactive methylene or methyl groups, *e.g.*, malononitrile, nitromethane, β-ketoesters and β-diketones, add via their active methylene or methyl groups to the 9,10-positions of acridine (VII) under *non-catalytic conditions* to give good yields of the corresponding 9-substituted acridans which can then be dehydrogenated to 9-substituted acridines. These workers did not study the addition of simple ketones,




I II I




III base = $CH_3Li, NaNH_2, NaN(C_3H_7\text{-}i)_2$

$$9\text{-AcrCH}_2\text{Li} + \text{RCO}_2\text{CH}_3 \longrightarrow \text{LiOH}_3 + 9\text{-AcrCH}_2\text{COR} \quad (2)$$

II III

$$\text{II} + \text{III} \longrightarrow \text{I} + (9\text{-AcrCHCOR})^-\text{Li}^+ \quad (3)$$

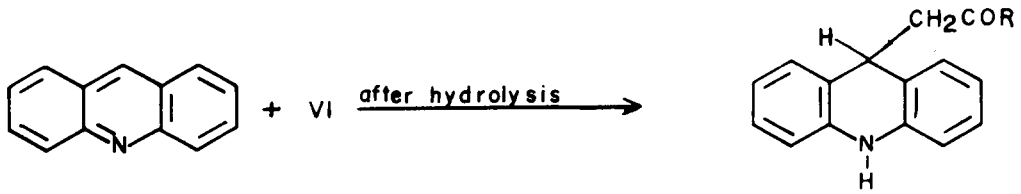
IV

$$\text{IV} \xrightarrow{\text{hydrolysis}} \text{III} \quad (4)$$

9-Acr = 9-acridinyl group

$$\text{RCOCH}_3 + \text{NaNH}_2 \xrightarrow{\text{l. NH}_3} (\text{RCOCH}_2)^-\text{Na}^+ + \text{NH}_3 \quad (5)$$

V VI




(6)

VII VIII

$$\text{VIII} \xrightarrow{\text{dehydrogenate}} \text{III} \quad (7)$$

*e.g.*, acetophenone and other methyl ketones, to VII. It would be anticipated that the *free methyl ketones* (as contrasted with their anions), whose $\alpha$-hydrogen atoms are not as labile as the methylene or methyl hydrogen atoms in the compounds studies by Kröhnke and Honig (12) would not be expected to readily undergo 9,10-addition to VII. It has also been found (13) that mixtures of VII, ammonium thiocyanate and acetophenone, acetone, methyl ethyl ketone or methyl isobutyl ketone give the corresponding alkyl 9-acridinylmethyl ketones in low yields. It is also of interest to note (14) that a series of aliphatic and aromatic Grignard reagents react under drastic conditions (sealed tube at 100°) with VII by 9,10-addition to give high yields of the corresponding 9-substituted acridans which were dehydrogenated to the corresponding acridines.

It has now been found that the sodium derivatives (VI) of a series of methyl ketones (V) (equation 5) undergo 9,10-addition to VII to give the corresponding 9-acridanylmethyl ketones (VIII) (equation 6), which can be dehydrogenated (equation 7) by aqueous ferric chloride solution or lead tetraacetate in benzene to the corresponding 9-acridinylmethyl ketones (III) as shown in the following scheme.

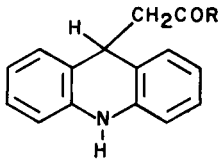
TABLE I

9-Acridinylmethyl Ketones, 9-AcrCH$_2$COR

| Compound | R | Yield, % | Method | M.P., °C | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $C_6H_5$ | 82.7 (a, b) 82.6 (b) | A (c) | | | | | | | | |
| | | 41.4 | B-1 (d) | | | | | | | | |
| | | 82.5 | B-2 (e) | 240-242 (f, g) | $C_{21}H_{15}NO$ | 84.85 | 84.85 | 5.05 | 5.03 | 4.72 | 4.97 |
| 2 | $C_6H_5$ (h) | 58.7 | B-1 | 154-156 (i) | $C_{22}H_{17}NO$ | 84.86 | 84.70 | 5.50 | 5.71 | 4.50 | 5.84 |
| 3 | 2-$C_5H_4N$ (j) | 70.0 | B-1 | 160-162 (i) | $C_{20}H_{14}N_2O$ | 80.52 | 80.66 | 4.73 | 4.86 | 9.39 | 9.35 |
| 4 | 3-$C_5H_4N$ (j) | 58.5 | B-1 | 202-203 (i) | | | 80.59 | | 4.90 | | 9.21 |
| 5 | 4-$C_5H_4$ (j) | 57.0 | B-1 | 207-209 (i) | | | 80.38 | | 4.96 | | 9.18 |
| 6 | $C_4H_3O$ (k) | 84.0 (l) | A (m) | 178-180 (i) | $C_{19}H_{13}O_2N$ | 79.43 | 79.26 | 4.56 | 4.81 | 4.88 | 4.53 |
| 7 | $C_4H_3S$ (n) | 86.7 (o) | A (p) | | | | | | | | |
| | | 69.2 | B-2 | 216-217 (f) | $C_{19}H_{13}ONS$ (q) | 75.22 | 75.39 | 4.32 | 4.42 | 4.62 | 4.64 |
| 8 | i-$C_3H_7$ (r) | 41.3 (r, s) | A (p) | | | | | | | | |
| | | 100.0 | B-2 | 131-132.5 (t) | $C_{18}H_{17}NO$ | 82.09 | 82.02 | 6.51 | 6.70 | 5.32 | 5.62 |
| 9 | i-$C_4H_9$ | 89.3 | B-2 | 143.5-145.5 (t, u) | $C_{19}H_{19}NO$ | 82.27 | 82.49 | 6.90 | 7.04 | 5.05 | 5.29 |
| | | | | Oximes | | | | | | | |
| 1a | | | | 254-256 dec. (v) | $C_{21}H_{16}N_2O$ | 80.75 | 81.04 | 5.16 | 5.25 | 8.97 | 8.92 |
| 2a | | | | 227-228 (v) | $C_{22}H_{18}N_2O$ | 80.96 | 80.96 | 5.56 | 5.79 | 8.58 | 8.54 |
| 3a | | | | 216-218 (v) | $C_{20}H_{15}N_3O$ | | | | | 13.41 | 13.68 |
| 4a | | | | 247.0-247.5 dec. (v) | | | | | | | 13.43 |
| 5a | | | | 259.0-259.5 dec. (v) | | | | | | | 13.44 |
| 6a | | | | 254.0 dec. (v) | $C_{19}H_{14}N_2O_2$ | 75.48 | 75.30 | 4.67 | 4.86 | 9.27 | 9.45 |
| 7a | | | | 237-239 dec. (v) | $C_{19}H_{14}N_2OS$ (w) | 71.67 | 71.64 | 4.43 | 4.62 | 8.80 | 8.52 |
| 8a | | | | 147-149 (v) | $C_{18}H_{18}N_2O$ | 77.67 | 77.41 | 6.52 | 6.65 | 10.07 | 10.09 |
| 9a | | | | x | | | | | | | |

(a) A 2:2:1 molar ratio of 9-methylacridine to phenyllithium to methyl benzoate was used. In all other reactions performed by method A a 1:1:1 molar ratio of reactants was used. (b) A 12.0% yield of 9-methyl-9-phenylacridan (A), m.p. 96.5-98.0° (from *n*-hexane, lit value (14), 96°), was obtained. *Anal.* Calcd. for $C_{20}H_{17}N$: C, 88.56; H, 6.27; N, 5.47. Found: C, 88.39; H, 6.45; N, 5.63. (c) Method A = acylation of 9-acridinylmethyllithium with the appropriate methyl or ethyl ester. (d) Method B-1 = dehydrogenation of the corresponding 9-acridanyl ketone by Pb(OAc)$_4$ in benzene. (e) Method B-2 = dehydrogenation of the corresponding 9-acridanyl ketone by $FeCl_3$ in HCl. (f) Recrystallized from benzene. (g) Lit. value (see ref. 13), 239-241°. (h) $CH_2COR$ is replaced by $CH(CH_3)COR$. (i) Recrystallized from a benzene-heptane mixture. (j) 2-$C_5H_4N$, 3-$C_5H_4N$ and 4-$C_5H_4N$ = 2-, 3- and 4-pyridyl radicals, respectively. (k) $C_4H_3O$ = 2-furyl radical. (l) An 8.7% yield of A was also obtained. (m) Methyl ester was used as acylating agent. (n) $C_4H_3S$ = 2-thienyl radical. (o) A 12.7% yield of A was also obtained. (p) Ethyl ester was used as the acylating agent. (q) % S: Calcd: 10.57; Found: 10.71. (r) A 12.0% yield of A was also obtained. (s) Determined by quantitative infrared analysis of the reaction mixture since the hydrochloride of the product did not precipitate when the reaction was quenched by being poured onto hydrochloric acid. (t) Recrystallized from 60-90° petroleum ether. (u) Lit. value (see ref. 13), 142-143°. (v) Recrystallized from 95% ethanol. (w) % S: Calcd: 10.07; Found: 10.09. (x) Did not give a crystalline oxime.

TABLE II




9-Acridanylmethylketones,

| R | Yield, % | M.P., °C | Formula | Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|---|---|
| $C_6H_5$ | 68.5 | 169-171 (a) | $C_{21}H_{17}NO$ | 84.25 | 84.53 | 5.72 | 5.74 | 4.68 | 4.81 |
| $C_6H_5$ (b) | 50.0 | 136.5-138 (c) | $C_{22}H_{19}NO$ | 84.31 | 84.21 | 6.11 | 6.16 | 4.47 | 4.23 |
| 2-$C_5H_4N$ | 77.5 | 157-159.5 (a) | $C_{20}H_{16}N_2O$ | 79.98 | 79.91 | 5.37 | 5.43 | 9.33 | 9.50 |
| 3-$C_5H_4N$ | 81.7 | 170-172 (a) | | | 80.32 | | 5.51 | | 9.15 |
| 4-$C_5H_4N$ | 33.5 | 176-178 (d) | | | 80.07 | | 5.38 | | 9.61 |
| $C_4H_3S$ (e) | 50.0 | 163-164 (f) | $C_{19}H_{15}NOS$ | 74.75 | 74.58 | 4.92 | 5.26 | 4.59 | 4.59 |
| i-$C_3H_7$ | 44.0 | 122-124 (g) | $C_{18}H_{19}NO$ | 81.51 | 81.54 | 7.17 | 7.26 | 5.29 | 5.05 |
| i-$C_4H_9$ | 57.0 | 116-118 (g) | $C_{19}H_{21}NO$ | 81.68 | 81.54 | 7.58 | 7.55 | 5.01 | 5.19 |

(a) Recrystallized from benzene. (b) $CH_2COR$ is replaced by $CH(CH_3)COR$. (c) Recrystallized from a benzene-*n*-hexane mixture. (d) Recrystallized from a benzene-ethanol mixture. (e) $C_4H_3S$ = 2-thienyl radical. (f) Recrystallized from ethyl ether. (g) Recrystallized from an ether-petroleum ether mixture.

The ketones (VIII, R = $CH_3$ and $C_2H_5$) could not be isolated when the sodium derivatives of acetone and methyl ethyl ketone, respectively, were condensed with VII. Although a reaction occurred in each case to give solid materials which contain carbonyl groups, the materials melted over a wide range and pure compounds could not be isolated. It is possible that the ketones formed self-condensation products which then underwent 9,10-addition to VII. The acridanyl ketones which were prepared are listed in Table II while the acridinyl ketones (III) which were prepared by dehydrogenating the ketones (VIII) appear in Table I. It can be seen that the three isomeric ketones (III), 9-picolinylmethyl-, 9-nicotinoylmethyl- and 9-isonicotinoylmethyl acridine, which could not be prepared by the acylation of II with the isomeric methyl pyridinecarboxylates have been made in fair to good yield by the route VI + VII → VIII → III. It should also be noted that the ketone (III, R = $i$-$C_3H_7$) is obtained in essentially the same overall yield by the acylation of II with ethyl isobutyrate and by the 9,10-addition of sodiomethyl isopropyl ketone to VII followed by the dehydrogenation of the acridan intermediate.

Since Eisleb (15) reported that ethyl α-(9-acridinyl)-acetoacetate can be cleaved by dilute sulfuric acid to 9-acridinylacetone, it was of interest to determine whether the β-ketoester route can be used to prepare other ketones containing the 9-acridinylmethyl radical. Hence, Krŏhnke and Honig's (12) method was used for preparing ethyl α-(9-acridinyl)isonicotinoyl acetate (IX) and ethyl α-(9-acridinyl)benzoylacetate (X). However, when IX was refluxed with dilute hydrochloric acid or sodium hydroxide it was cleaved to 9-methylacridine in 62% and 52% yields, respectively and no 9-(isonicotinoylmethyl)acridine was obtained. When X was refluxed with 10% sulfuric acid only a 6.3% yield of the desired product, 9-phenacylacridine, was obtained. Therefore, the cleavage of β-ketoesters containing the 9-acridinyl radical is not a good route to the synthesis of 9-acridinylmethyl ketones.

Preparation of 9-Methylacridine.

Several known methods were used to obtain 9-methylacridine. The procedure of Campbell *et al.* (16) starting with 9-chloroacridine (17) gave a mixture of 9-methylacridine (55%, m.p. 116-118° from ethyl acetate) and acridone (28.5%, m.p. 350-354°). The Bernthsen reaction (18) (interaction of diphenylamine, acetic acid and zinc chloride in an autoclave at 220-240° for 18 hours), gave 9-methylacridine (39.3%, m.p. 114-117°). When this reaction was effected at atmospheric pressure, a 13.5% yield of product was obtained. The Porai-Koshits and Kharkharov (19) modification of the Bernthsen reaction (using acetic anhydride in place of acetic acid) gave only a 10.9% yield of product as contrasted with the 70% yield which is claimed in the literature (19).

Typical Procedure for the Acylation of 9-Methylacridine with Esters.

Phenyllithium (0.15 mole) was prepared from bromobenzene (23.6 g., 0.15 mole), lithium ribbon (2.1 g., 0.3 mole) and 170 ml. of anhydrous ether in a 500-ml. three-neck Morton flask equipped with ground glass joints and fitted with a reflux condenser, a drying tube and an efficient stirrer. 9-Methylacridine 28.95 g., 0.15 mole) was added as a fine powder over a 10-min. period, 75 ml. of anhydrous ether being used to wash the 9-methylacridine into the reaction flask. The reaction mixture was then refluxed for 30 min. To the rapidly stirred, maroon-colored reaction mixture, methyl benzoate (20.4 g., 0.15 mole), dissolved in an equal volume of ether, was added over a 20-minute period so that the ether refluxed rapidly and the reaction mixture was refluxed for 30 min. Then, 30 ml. of water was added slowly and the reaction mixture was poured onto 37.5 ml. of 6 N hydrochloric acid and 188 g. of crushed ice. The hydrochloride of 9-phenacylacridine precipitated and was filtered. It was washed with warm dilute hydrochloric acid to dissolve any occluded 9-methylacridine hydrochloride. The damp product was thoroughly triturated with aqueous potassium hydroxide to liberate the 9-phenacylacridine, which was filtered, washed with distilled water and dried in a vacuum desiccator to give 9-phenacylacridine (18.4 g., 82.7%, m.p. 240-242°, fluffy, white crystals from benzene). Treatment of the product with 6 N hydrochloric acid gave its hydrochloride, m.p. 260-262° dec. The phases of the aqueous hydrochloric acid-ether filtrate described above were separated. The ether layer was extracted with three 100 ml. portions of 6 N hydrochloric acid, then washed with water and dried over calcium chloride. The ether was evaporated to give 17.5 g. of acid-insoluble material, which was distilled to give recovered methyl benzoate (10.5 g., 51.3%, b.p. 93-100° at 14 mm.). The 7.0 g. of residue was dissolved in a benzene-*n*-hexane solution and was chromatographed on a silica gel column to give 9-phenyl-9-methylacridan (5.0 g., 12.0%, m.p. 96.5-98°, white crystals from *n*-hexane). The remaining aqueous hydrochloric acid layer and water washings were combined and made basic with concentrated aqueous ammonia. The precipitated solid was filtered, washed thoroughly with water and dried in a vacuum desiccator to give recovered 9-methylacridine (13.7 g., 47.3%, m.p. 116-118° alone and when mixed with an authentic sample).

Typical Procedure for the 9,10-Addition of Sodio-Ketones to Acridine.

To sodium amide, prepared from sodium (4.6 g., 0.2 mole) in 200 ml. of anhydrous liquid ammonia (20), acetophenone (24.0 g., 0.2 mole) in an equal volume of anhydrous ether was added over a 10-min. period. After 20-30 min. of additional stirring, powdered acridine (0.2 mole, 35.8 g.) was added over a 10-min. period using about 30 ml. of anhydrous ether to wash the acridine from the sides of the flask into the reaction mixture. All the acridine had dissolved after about 2.5 hours. (With some of the other ketones, the reaction was more gradual, requiring up to six hours for the acridine to dissolve.) Then 125 ml. of anhydrous ether was added and the ammonia was allowed to evaporate overnight. To the resultant stirred ether suspension, 75 ml. of water was added slowly. The heavy precipitate which formed was filtered, washed with water and dried to give 9-phenacylacridan (39.5 g., 66%, m.p. 169-171° from benzene). The washings were combined with the filtrate and the aqueous layer was separated and extracted with ether. The combined ether layers were washed once with water and the aqueous layer and the washings were discarded. The combined ether extracts were extracted with three 150 ml. portions of 6 N hydrochloric acid (extract A) and then they were washed with water until neutral. The ether extracts were dried over calcium chloride and the solvent was removed to give a yellow, semi-solid, which was filtered on a fritted-glass filter to give an additional 1.5 g. (2.5%) of 9-phenacylacridan, m.p. 166-168°, the total yield of which was 68.5%. The combined hydrochloric acid extracts (extract A) were made basic with concentrated aqueous ammonia and the precipitated product was filtered, washed with water and dried in a vacuum desiccator to give recovered acridine (10.2 g., 28.5%, m.p. 107-108° alone and when mixed with an authentic sample). With proplophenone, methyl isopropyl ketone and methyl isobutyl ketone, the 9-acridanylmethyl ketones did not precipitate from the reaction mixture on hydrolysis. They were present in the acid-extracted ether residue mixed with unreacted starting ketone. In these cases the starting ketones and the ketonic products were separated by distilling the solvent and any liquid starting ketone and recrystallizing the solid residue.

Oxidation of 9-Acridanylmethyl Ketones to 9-Acridinylmethyl Ketones.

(a) *By ferric chloride.* A freshly prepared filtered solution of ferric chloride (9.7 g., 0.06 mole in about 40 ml. of distilled water) was added from a dropping funnel over a 5-min. period to a hot, rapidly stirred suspension of 9-phenacylacridan (6.0 g., 0.02 mole) in 400 ml. of 1 N hydrochloric acid. The reaction mixture was refluxed for four min. After cooling to room temperature, the solid was filtered, washed with water and dried. It weighed 5.5 g. and its infrared spectrum was identical with that of an authentic sample of 9-phenacylacridine hydrochloride. The product was triturated with aqueous 30% sodium hydroxide, filtered, washed with water and dried to give 9-phenacylacridine (4.9 g., 82.5%, m.p. 240-242° from benzene). (b) *by lead tetraacetate.* Benzene (300 ml.), pyridine (2.6 ml.) and 9-picolinylmethylacridan (6.0 g., 0.02 mole) were warmed with stirring until the acridan had dissolved. The solution was cooled to room temperature and then lead tetraacetate (8.8 g., 0.02 mole) was added with rapid stirring over a 5-min. period. The color of the mixture quickly changed from light yellow to light orange. Stirring was continued for one hour at room temperature. The mixture was filtered and the insoluble lead acetate was washed with a little benzene. The clear, light orange filtrate was washed with four 100 ml. portions of water and dried over calcium chloride. The benzene solution was concentrated to about 140 ml. and allowed to crystallize overnight at -5°. The buff colored crystals were filtered, washed with a benzene-petroleum ether mixture and dried to give 9-picolinylmethylacridine (3.05 g., 51.2%, m.p. 160-162° from a benzene-*n*-heptane mixture). Further concentration of the above filtrate to about 25 ml. gave an additional 1.11 g. (18.7%) of 9-picolinylmethylacridine, m.p. 160-162°.

Preparation of Ethyl α-(9-acridanyl)isonicotinoylacetate.

The method which Krŏhnke and Honig (12) used to prepare similar compounds was employed to synthesize this new β-ketoester. From a mixture of ethyl isonicotinoylacetate (2.3 g., 0.012 mole, m.p. 51-53°, prepared essentially according to the method of Burrus and Powell) (21) and acridine (2.1 g., 0.012 mole), which had been allowed to stand for three days at room temperature, there was obtained ethyl α-(9-acridanyl)isonicotinoylacetate (4.3 g., 97.7%, m.p. 94.5-95.5° from ethanol).

*Anal.* Calcd. for $C_{23}H_{20}N_2O_3$: C, 74.17; H, 5.41; N, 7.52. Found: C, 74.01; H, 5.43; N, 7.69.

Dehydrogenation of Ethyl α-(9-acridanyl)isonicotinoylacetate to Ethyl α-(9-acridinyl)isonicotinoylacetate (IX) and Attempts to Convert IX to 9-Isonicotinoylmethylacridine.

From the interaction of ethyl α-(9-acridanyl)isonicotinoylacetate (1.9 g., 0.005 mole), benzene (150 ml.), pyridine (0.5 ml.) and lead tetraacetate (2.2 g., 0.005 mole) there was obtained 1.9 g. of a light yellow, very viscous oil which was assumed to be ethyl α-(9-acridinyl)isonicotinoylacetate (IX). Although an elemental analysis of this β-ketoester was not performed, its infrared spectrum showed the absence of an N-H band at 3.1 microns and the presence of two new carbonyl bands at 5.7 and 6.1 microns and an enol-like broad hydroxyl band in the 3.0-3.5 micron region. Refluxing a sample of IX with a dilute

hydrochloric acid-ethanol mixture gave 9-methylacridine (m.p. 116-118°) in 62% yield. No 9-isonicotinoylmethylacridine was found. When another sample of IX was refluxed with dilute sodium hydroxide a 52% yield of 9-methylacridine (m.p. 116-118°) was obtained. Again no 9-isonicotinoylmethylacridine was isolated.

Conversion of Ethyl α-(9-acridinyl)benzoylacetate, X, to 9-Phenacylacridine.

Ethyl α-(9-acridinyl)benzoylacetate (1.2 g., prepared by the method of Kröhnke and Honig (12)) was refluxed in 10% sulfuric acid for one hour. The yellow crystals, which deposited on cooling, were filtered and washed with water. The still damp crystals were triturated with hot aqueous potassium hydroxide to liberate the 9-phenacylacridine (0.06 g., 6.3%, m.p. 240-242° alone and when mixed with an authentic sample).

Conversion of 9-Picolinylmethylacridine to 9-Methylacridine.

To 0.2 g. of 9-picolinylmethylacridine were added distilled water (3.0 ml.), 10% aqueous sodium hydroxide (3.0 ml.) and enough 95% ethanol to give a clear solution. The solution was heated on a steam bath for 25 minutes and cooled to room temperature. Water was added until the solution just became cloudy and the resultant mixture was allowed to crystallize overnight at -5°. The crystals were filtered, washed with aqueous ethanol and dried to give 9-methylacridine (0.1 g., 77.2%, m.p. 116-118° alone and when mixed with an authentic sample). When 3 ml. of dilute hydrochloric acid was used in place of the sodium hydroxide, 9-methylacridine (0.12 g., 92.7%, m.p. 115-117°) was obtained after liberating the free base from its hydrochloride with aqueous sodium hydroxide.

## REFERENCES

(1) This paper is based on part of the thesis presented by C. S. S. to the Graduate Faculty of the University of Pittsburgh in partial fulfillment of the requirements for the Ph.D. degree.

(2) C. Osuch and R. Levine, *J. Org. Chem.*, 22, 939 (1957).

(3) S. Raynolds and R. Levine, *J. Am. Chem. Soc.*, 82, 472 (1960).

(4) N. Fisher, C. S. Franklin, E. N. Morgan and D. J. Tivey, *J. Chem. Soc.*, 1411 (1958).

(5) T. D. Perrine, *J. Org. Chem.*, 25, 1516 (1960).

(6) V. V. Perekalin and A. S. Polyanskaya, *Zhur. Obshchei Khim.*, 27, 1933 (1957).

(7) C. T. Bahner, C. Cook, J. Dale, J. Fain, E. Franklin, J. C. Goan, W. Stump and J. Wilson, *J. Org. Chem.*, 22, 682 (1957).

(8) H. Lettré, J. Jungman and J. Salfeld, *Chem. Ber.*, 85, 397 (1952).

(9) K. Ziegler and H. Zeiser, *Ann.*, 485, 174 and 192 (1931).

(10) N. N. Goldberg and R. Levine, *J. Am. Chem. Soc.*, 77, 3647 (1955).

(11) N. N. Goldberg, L. B. Barkley and R. Levine, *ibid.*, 73, 4301 (1951).

(12) F. Kröhnke and H. L. Honig, *Ann.*, 624, 97 (1959).

(13) E. Hayashi, *Yakugaku Zasshi*, 79, 969 (1959).

(14) E. Hayashi, S. Ohsumi and T. Maeda, *ibid.*, 79, 967 (1959).

(15) O. Eisleb., *Med. u. Chem., Abhandl. med.-chem. Forschungslatten, I. G. Farbenind.*, 3, 41 (1936); *C. A.* 31, 5802 (1937).

(16) A. Campbell, C. S. Franklin, E. N. Morgan and D. J. Tivey, *J. Chem. Soc.*, 1145 (1958).

(17) A. Albert and B. Ritchie, Org. Synth., Vol. 22, John Wiley and Sons, New York, N. Y., 1942, p. 5.

(18) A. Bernthsen, *Ann.*, 224, 1 (1884).

(19) A. E. Porai-Koshits and A. A. Kharkharov, *Bull. acad. Sci. U.R.S.S. classe sci. chim.*, 243 (1944); *C. A.* 39, 1631 (1945).

(20) S. R. Harris and R. Levine, *J. Am. Chem. Soc.*, 70, 3360 (1948).

(21) H. O. Burrus and G. Powell, *ibid.*, 67, 1468 (1945).

Received February 21, 1964

Pittsburgh 13, Pennsylvania